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EXAMINER	
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte HARRY R. DAVIS
and
TEDDY KOSOGLOU

Appeal 2007-4484
Application 10/057,534[1]
Technology Center 1600

Decided: April 11, 2008

Before TEDDY S. GRON, CAROL A. SPIEGEL, and DEMETRA MILLS, *Administrative Patent Judges*.

SPIEGEL, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] Application 10/057,534 ("the 534 application") filed 25 January 2002, said to claim priority benefit of the 26 January 2001 filing date of provisional application 60/264,600 and the 21 September 2001 filing date of provisional application 60/323,842. The real party-in-interest is said to be Schering Corporation (Appellant's Brief Under 37 C.F.R. § 1.192 filed 2 August 2005 ("Br."), 1).

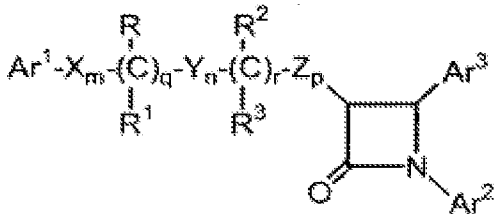
I. Statement of the Case

Harry R. Davis and Teddy Kosoglou ("Appellants") appeal under 35 U.S.C. § 134 from a final rejection of claims 1-3, 5, 6, 8-11, 28, 31-33, 35, 36, 70-72, 74-77, 79, and 80 (Ans.[2] 2). Claim 7 has been cancelled (Br. 1; Ans. 2). Claims 4, 12-27, 29, 30, 34, 37-69, 73, 78, and 81, the only other pending claims, have been withdrawn from consideration (Ans. 2). We have jurisdiction under 35 U.S.C. § 6(b). We AFFIRM.

The subject matter on appeal relates to compositions and therapeutic combinations comprising at least one bile acid sequestrant, about 10 mg of at least one structurally identified sterol absorption inhibitor, and, optionally, at least one cholesterol biosynthesis inhibitor, as well as methods of use thereof for treating hyperlipidemic conditions.

Claims 1 and 8 are illustrative and read:

> 1. A composition comprising:
>
> (a) at least one bile acid sequestrant; and
>
> (b) about 10 milligrams of at least one sterol absorption inhibitor represented by Formula (I):



(I)

> or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers thereof, or prodrugs of the

[2] Examiner's Answer mailed 24 October 2005 ("Ans.").

compounds of Formula (I) or of the isomers, salts or solvates thereof, wherein in Formula (I) above:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of -CH_2-, -CH (lower alkyl)- and -C(dilower alkyl)-;

R and R^2 are independently selected from the group consisting of -OR^6, -$O(CO)R^6$, -$O(CO)OR^9$ and -$O(CO)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR^6, -$O(CO)R^6$, -$O(CO)OR^9$, -$O(CH_2)_{1-5}OR^6$, -$O(CO)NR^6R^7$, -NR^6R^7, -$NR^6(CO)R^7$, -$NR^6(CO)OR^9$, -$NR^6(CO)NR^7R^8$, -$NR^6SO_2R^9$, -$COOR^6$, -$CONR^6R^7$, -COR^6, -$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, -$O(CH_2)_{1-10}$-$COOR^6$, -$O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, -CH=CH-$COOR^6$, -CF_3, -CN, -NO_2 and halogen;

> R^5 is 1-5 substituents independently selected from the group consisting of -OR^6, -$O(CO)R^6$, -$O(CO)OR^9$, -$O(CH_2)_{1-5}OR^6$, -$O(CO)NR^6R^7$, -NR^6R^7, -$NR^6(CO)R^7$, -$NR^6(CO)OR^9$, -$NR^6(CO)NR^7R^8$, -$NR^6SO_2R^9$, -$COOR^6$, -$CONR^6R^7$, -COR^6, -$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, -$O(CH_2)_{1-10}$-$COOR^6$, -$O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and -CH=CH-$COOR^6$;
>
> R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and
>
> R^9 is lower alkyl, aryl or aryl-substituted lower alkyl.
>
> 8. The composition according to claim 1, further comprising at least one cholesterol biosynthesis inhibitor.

Claim 3 ultimately depends from claim 1 and recites a composition "wherein the at least one bile acid sequestrant comprises cholestyramine." Claim 11 ultimately depends from claim 8 and recites a composition "wherein the at least one cholesterol biosynthesis inhibitor comprises at least one HMG CoA reductase inhibitor" which is simvastatin. [Br. 21-23, "CLAIM APPENDIX."]

In response to an election of species requirement in the Office Action of July 16, 2003, Appellants elected cholestyramine as the bile acid sequestrant, ezetimibe as the sterol absorption inhibitor, and simvastatin as the cholesterol biosynthesis inhibitor for examination (Br. 7-8). Thus, compositions, combinations, and methods including these three species are before us.

The Examiner relies on the following references[3] as evidence of unpatentability:

Dechow	US 4,837,255	Jun. 6, 1989
Albright	US 5,300,288	Apr. 5, 1994
Davis	US 5,661,145	Aug. 26, 1997
Rosenblum	US 5,846,966	Dec. 8, 1998

The Examiner has rejected claims 1-3, 5, 6, 8-11, 28, 31-33, 35, 36, 70-72, 74-77, 79, and 80 under 35 U.S.C. § 103(a) as unpatentable over Rosenblum in view of Albright, Dechow, and Davis (Ans. 2-3).

II. Findings of Fact ("FF")

The following findings of fact and any set out in the Discussion are supported by a preponderance of the evidence of record.

A. The 534 Application

[1] In one embodiment, the 534 specification describes compositions, pharmaceutical compositions, therapeutic combinations, kits and methods of treatment using the same comprising at least one bile acid sequestrant and at least one substituted azetidinone sterol absorption inhibitor or substituted ß-lactam sterol absorption inhibitor (Spec. 23:21-26).

[2] In a preferred embodiment, the sterol inhibitor is ezetimibe, i.e., 1-(4-fluorophenyl)-3(R)-[3(R)-(4-fluorophenyl)-3-hydroxypropyl)]-4(s)-(4-hydroxyphenyl)-2-azetidinone (Spec. 30:9-17).

[3] According to the 534 specification,

> [t]he daily dose of the sterol absorption inhibitor(s) preferably ranges from about 0.1 to about 1000 mg per day, and more preferably about 0.25 to about 50 mg/day, given in a single dose or 2-4 divided

[3] No references to *et al.* are made in this opinion.

> doses. The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient. [Spec., 65:23-27.]

[4] In another embodiment, the composition or treatment further comprises one or more cholesterol biosynthesis inhibitors co-administered, or in combination, with the bile acid sequestrant(s) and sterol absorption inhibitor(s) (Spec. 66:4-6).

[5] Suitable cholesterol biosynthesis inhibitors include competitive inhibitors of HMG CoA reductase such as simvastatin (Spec. 66:7-15).

[6] The compositions and combinations of the 534 application are said to be useful "for treating hyperlipidemic conditions . . . associated with atherosclerosis, hypercholesterolemia and other vascular conditions in mammals" (Spec. 1:12-15).

B. Rosenblum

[7] Rosenblum discloses using a combination of a hydroxy substituted azetidinone and cholesterol biosynthesis inhibitor for treating and preventing atherosclerosis (Rosenblum 1:19-24).

[8] Suitable cholesterol biosynthesis inhibitors include HMG CoA reductase inhibitors such as simvastatin (Rosenblum 6:37-41; claim 3).

[9] Suitable hydroxy substituted azetidinones include ezetimibe (Rosenblum 32:45-58 (product "6B"); claim 5).

[10] According to Rosenblum, the daily hypocholesteremic dose of a hydroxy-substituted azetidinone cholesterol absorption inhibitor

> is about 0.1 to about 30 mg/kg of body weight per day, preferably about 0.1 to about 15 mg/kg. For an average body weight of 70 kg, the dosage level is therefore from about 5 mg to about 1000 mg of drug per day, given in a single dose or 2-4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient. [Rosenblum 21:17-26.]

[11] Rosenblum claim 5 recites a pharmaceutical composition for the treatment or prevention of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising a combination of ezetimibe and one of lovastatin, pravastatin, fluvastatin, simvastatin or atorvastatin.

C. Albright

[12] According to Albright, "[t]wo materials which are known to be effective in lowering blood cholesterol levels by acting on bile acids in the digestive tract are cholestyramine and cholestipol" (Albright 2:2-5).

D. Dechow

[13] Dechow discloses improving the palatability of cholestyramine by providing it in a hypocholesterolemic gel formulation for oral administration (Dechow 1:8 through 2:9).

E. Davis

[14] Davis discloses using a combination of a cholesterol biosynthesis inhibitor, e.g., the HMG CoA reductase inhibitor simvastatin, and a

ß-lactam cholesterol absorption inhibitor[4] for reducing plasma cholesterol levels in a mammal in need thereof (Davis 2:2-55).

III. Discussion

A claimed invention is not patentable if the subject matter of the invention would have been obvious to a person having ordinary skill in the art at the time the invention was made. 35 U.S.C. § 103(a); *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007); *Graham v. John Deere Co.*, 383 U.S. 1 (1966). Facts relevant to a determination of obviousness include (1) the scope and content of the prior art, (2) any differences between the claimed invention and the prior art, (3) the level of ordinary skill in the art, and (4) any relevant objective evidence of obviousness or nonobviousness. *KSR*, 127 S.Ct. at 1734; *Graham*, 383 U.S. at 17-18.

The question under 35 U.S.C. § 103 is not merely what the prior art references expressly teach, but what the combined teachings of the references would have suggested to those of ordinary skill in the art. *In re Keller*, 642 F.2d 413, 425 (CCPA 1981). A combination of known elements with no change in their respective functions is likely to be obvious when it does no more than yield predictable results. *KSR,* 127 S.Ct. at 1739-41. "[A] reasonable expectation of success, not absolute predictability", supports a conclusion of obviousness. *In re Longi*, 759 F.2d 887, 897 (Fed. Cir. 1985).

One of ordinary skill in the art is presumed to have skills apart from what the prior art references expressly disclose. *In re Sovish*, 769 F.2d 738,

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[4] Ezetimibe is a ß-lactam containing fluorine in the side chain. *See e.g.,* Konev et al., "A simple route to side-chain fluorinated ß-lactams from ring-fluorinated aziridines," *Journal of Fluorine Chemistry*, Vol. 128 (2007):114-119.

743 (Fed. Cir. 1985). A person of ordinary skill is also a person of ordinary creativity, not an automaton. *KSR*, 127 S.Ct. at 1742.

The subject matter on appeal before us is directed to compositions and combinations comprising cholestyramine and about 10 mg of ezetimibe, and optionally simvastatin, and methods of use thereof for treating or preventing hyperlipidemic conditions, e.g., atherosclerosis, hypercholesterolemia and other vascular conditions.

The Examiner found that Rosenblum teaches the combination of ezetimibe and simvastatin, but not the combination of either cholestyramine and ezetimibe or cholestyramine, ezetimibe and simvastatin, for use in treating hypercholesterolemia. The Examiner found that Rosenblum teaches that the daily dosage of the ezetimibe is about 5 mg to about 1000 mg, given in a single dose or 2-4 divided doses, and that the exact dosage depends on various conditions. The Examiner also found that Albright and Dechow teach using cholestyramine for treating hypercholesterolemia and that Davis teaches the combination of a ß-lactam cholesterol absorption inhibitor and simvastatin for use in treating hypercholesterolemia. [Ans. 4-5.]

The Examiner concluded that it would have been obvious to one of ordinary skill in the art to make a blood cholesterol lowering composition comprising a combination of (a) ezetimibe and cholestyramine or (b) ezetimibe, cholestyramine, and simvastatin since each agent individually is taught in the prior art for use in lowering cholesterol and the prior art would have taught persons having ordinary skill in the art to combine different cholesterol lowering agents for treating hypercholesterolemia (Ans. 5-6). The Examiner further concluded that use of about 10 mg of ezetimibe in the modified composition of Rosenblum would have been a matter of routine

optimization and prima facie obvious to a person having ordinary skill in the art (Ans. 5-6).

Appellants argue that the cited prior art does not suggest combining about 10 mg of ezetimibe with cholestyramine as recited in claim 1 (Br. 14) or about 10 mg of ezetimibe with cholestyramine and simvastatin as recited in claim 8 (Br. 18) and each of these three agents have a different mechanism of action (Br. 15 and 18).[5] Appellants further argue that there would have been no motivation to use the claimed amount of about 10 mg of ezetimibe (Br. 16 and 20).

Here, the cited prior art teaches that each of cholestyramine (Albright and Dechow), ezetimibe (Rosenblum and Davis), and simvastatin (Rosenblum and Davis) are known lipid lowering agents. The prior art also teaches that ezetimibe and simvastatin are combinable in a single composition for lowering blood lipid (cholesterol) concentrations (Rosenblum and Davis). Therefore, we agree with the Examiner, that based on the teachings of the applied prior art, it would have been *prima facie* obvious to one of ordinary skill in the art to combine two or all three of the three known lipid lowering agents in a single composition useful for treating hyperlipidemia and diseases associated with hyperlipidemia. *In re Kerkhoven*, 626 F.2d 846, 850 (CCPA 1980) ("It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to

[5] Appellants' arguments directed to combinations of other lipid management components are immaterial since only combinations comprising ezetimibe, cholestyramine, and simvastatin are before us on appeal. Similarly, Appellants' arguments specifically directed to the subject matter of claims 23, 24, and 27 (Br. 19) are immaterial since none of claims 23, 24, and 27 are on appeal before us.

be used for the very same purpose. * * * As this court explained in [In re] Crocket [279 F.2d 274, 276-77 (CCPA 1960], the idea of combining them flows logically from their having been individually taught in the prior art. In the case at bar, appealed claims 2-4, 9 and 14 require no more than the mixing together of two conventional spray-dried detergents. Thus, the claims set forth a prima facie obvious subject matter."). The fact that one, two or three of these lipid lowering agents act by different mechanisms is not persuasive of nonobviousness since one of ordinary skill in the art would have reasonably expected the combinations of ezetimibe and cholestyramine and ezetimibe, cholestyramine, and simvastatin to reduce or lower lipids. Indeed, we find that one of ordinary skill in the art should have known that agents having different mechanisms for the same action would, in combination, often require lower doses than when administered individually for that action.[6]

We also agree with the Examiner that it would have been prima facie obvious to optimize the daily hypocholesteremic dose disclosed by Rosenblum. Optimization flows from the "normal desire of scientists or artisans to improve upon what is already generally known." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003); *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). "[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980). Appellants have not directed us to evidence showing that more than routine experimentation would be required to optimize the amount of ezetimibe in the claimed compositions/combinations, especially given the range of the daily

[6] See e.g., the discussion of drug combinations in *In re Diamond*, 360 F.2d 214, 217 (CCPA 1966).

hypocholesteremic dose disclosed by Rosenblum. *Rohm and Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997) (nothing in the rules or in jurisprudence requires the fact finder to credit unsupported or conclusory assertions); *In re Schulze*, 346 F.2d 600, 602 (CCPA 1965) (argument in the brief does not take the place of evidence of record).

Accordingly, based on the foregoing, we AFFIRM the rejection of claims 1-3, 5, 6, 8-11, 28, 31-33, 35, 36, 70-72, 74-77, 79, and 80 under 35 U.S.C. § 103(a) as unpatentable over Rosenblum in view of Albright, Dechow, and Davis.

IV. Order

Upon consideration of the record, and for the reasons given, it is

ORDERED that the decision of the Examiner rejecting claims 1-3, 5, 6, 8-11, 28, 31-33, 35, 36, 70-72, 74-77, 79, and 80 under 35 U.S.C. §103(a) as obvious over Rosenblum in view of Albright, Dechow, and Davis is AFFIRMED; and,

FURTHER ORDERED that no time period for taking any subsequent action in connection with this appeal may be extended under 35 U.S.C. § 1.136(a) (2006).

AFFIRMED

MAT

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